



# Secondary pneumonias in critically ill patients with COVID-19: risk factors and outcomes

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## Purpose of review

The aim of this review is to provide an overview of the current evidence of secondary pneumonias in COVID-19 patients, its incidence, risk factors and impact outcomes.

## Recent findings

Early studies reported low incidence of hospital-acquired infections in COVID-19 patients. More recent large studies clearly showed that the incidence of secondary pneumonias was markedly high in patients under mechanical ventilation. Duration of mechanical ventilation, acute respiratory distress syndrome, prone position and male sex were identified as risk factors. The adjunctive therapy with steroids and immunomodulators were associated with a higher risk of pneumonia and invasive pulmonary Aspergillosis. Although secondary pneumonias seemed to be associated with poor outcomes, namely mortality, in comparison with influenza, no difference was found in heterogeneity of outcomes. Immunosuppressive therapy has been studied in several observational and randomized trials with conflicting results and the true impact on superinfections, namely secondary pneumonias, has not been properly assessed.

## Summary

According to the current evidence, COVID-19 patients are at an increased risk of secondary pneumonias. The impact of immunosuppressive therapies on superinfections is yet to be determined. Further studies are needed to assess the true risk of secondary infections associated with immunosuppressive therapies and to identify preventive strategies.

## Keywords

COVID-19, immunosuppressive therapies, outcomes, risk factors, ventilator associated pneumonia, ventilator associated tracheobronchitis

## INTRODUCTION

The COVID-19 pandemic with millions of patients and deaths worldwide has caused a marked shift in the amount and speed at which scientific research is conducted and shared. Even though huge progresses have been achieved in different areas, from the supportive care to the prevention, COVID-19 remains a new disease yet with important gaps in the comprehension of pathophysiology that could lead to the identification of new potential targets for drug development.

COVID-19 is a common cause of acute hypoxic respiratory failure and acute respiratory distress syndrome (ARDS) with the frequent need of invasive mechanical ventilation [1]. Moreover, from the beginning of the pandemic, it was clear that these patients presented long durations of mechanical ventilation, often in prone position, treated in strained healthcare systems with high demand for ICU beds, sometimes with health professionals recruited from non-ICU departments [1,2<sup>\*\*\*</sup>]. As a

result, these patients are at increased risk of developing ventilator-associated lower respiratory tract infections (VA-LRTI), either ventilator-associated pneumonia (VAP) or ventilator-associated tracheobronchitis (VAT).

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## KEY POINTS

- The incidence of secondary pneumonias in COVID-19 patients is significantly higher when compared with influenza; but the rates of MDR pathogens are lower.
- Apart from the known risk factors for secondary pneumonias, immunosuppressive therapies were identified as potential risk factors for pneumonia and invasive pulmonary Aspergillosis.
- Although secondary pneumonias seemed to be associated with poor outcomes, namely mortality, in comparison with influenza, no difference was found in heterogeneity of outcomes.
- The use of immunosuppressive therapy has been done and studied in several observational and randomized trials with conflicting results and the true impact on superinfections, namely secondary pneumonias, need to be further assessed.

Finally, and contrary to the initial thoughts, COVID-19 patients present low levels of cytokines namely interleukin (IL) 6 [3,4], high levels of complement activation with C5a release [5] as well as marked depression of cellular immunity [6,7]. These findings together with the potential impact of SARS-CoV-2 infection *per se* on lung mucosal immunity alongside with the use of immunosuppressive drugs, like corticosteroids, could increase even further the risk of VA-LRTI [8<sup>\*</sup>].

With the available literature, the aim of this review is to provide a clear overview of the current evidence of VA-LRTI in COVID-19 patients, its incidence, risk factors and impact outcomes.

### Ventilator-associated tracheobronchitis / ventilator-associated tracheobronchitis in COVID-19 vs. influenza

Early studies reported low incidence (10–13%) of hospital-acquired infections, including ICU-acquired pneumonia and VAP, in COVID-19 patients [9,10]. However, no clear definition was given for hospital-acquired pneumonia or VAP diagnosis, as well as whether quantitative microbiological confirmation was required for its diagnosis. Further, a relatively small number of SARS-CoV-2 patients were included in these studies, no control group was used, and no adjustment was performed for confounding factors. Several recent single-centre studies, using a strict definition and quantitative microbiology, reported higher incidence of VAP in COVID-19 patients, ranging from 44 to 86% [11–15]. The highest rates were observed in patients with ARDS [14], especially those treated with extracorporeal membrane oxygenation

(ECMO) [15]. Our group performed a large retrospective multicentre European coVAPid study to determine the incidence of VA-LRTI [2<sup>\*\*</sup>]. COVID-19 patients were compared with influenza patients, and patients with no viral infection at ICU admission, and VA-LRTI definition was based on clinical, radiological and quantitative microbiology in all patients. A total of  $N=1576$  patients receiving mechanical ventilation for more than 48 h were included (568 in SARS-CoV-2, 482 in influenza and 526 in no viral infection groups). We found that the cumulative incidence of VA-LRTI was significantly higher in SARS-CoV-2 patients, as compared with those with influenza, or no viral infection [50.5, 30.3 and 25.3%; respectively; adjusted sub hazard ratio (aSHR) 1.6 (95% confidence interval, 95% CI) 1.27–2)] for SARS-CoV-2 vs. influenza; aSHR 1.65 95%CI 1.22–2.22) for SARS-CoV-2 vs. no viral infection].

Several explanations could be provided for the high incidence of VA-LRTI in COVID-19 patients, including the long duration of invasive mechanical ventilation, the high incidence of ARDS, and the common use of corticosteroids and immunosuppressive treatments. Another possible explanation is the specific pulmonary lesions related to SARS-CoV-2 infection and the altered immunity, which might promote bacteria colonization and infection.

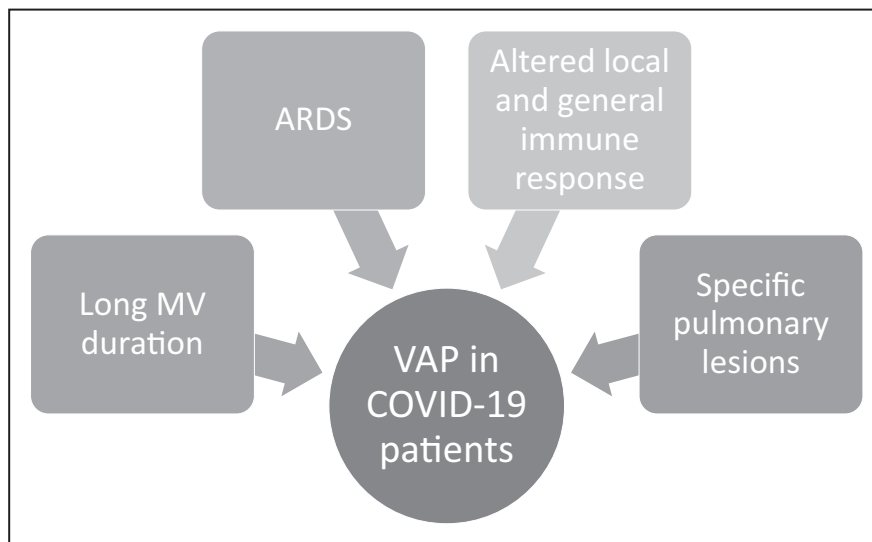
### Risk factors for VA-LRTI

Several variables have been identified as risk factors for VA-LRTI [16,17]. The most significant risk factor is endotracheal intubation and its duration [18,19]. But, other risk factors have been identified from multivariate analysis of observational studies, that could be divided into nonmodifiable, for example older age, multiple trauma, chronic lung disease, ARDS, depressed level of consciousness at the time of intubation and aspiration, chest and abdominal surgery and in modifiable risk factors, for example drugs that increase gastric pH, patient positioning, tracheal tube cuff pressure, selective oral decontamination, sedation and neuromuscular blocking agents, steroids [20,21<sup>\*</sup>].

Recent guidelines proposed several approaches to prevent or reduce the risk of VA-LRTI [22,23]. In a word, almost all strategies aim to decrease the duration of mechanical ventilation and intubation as well as to reduce the oropharyngeal bacterial load and the risk of tracheal aspiration.

It is now clear that COVID-19 patients under invasive mechanical ventilation present a high risk of VA-LRTI [1,2<sup>\*\*</sup>, 11,14,24,25]; however, the reasons for this high incidence are not immediately straightforward (Fig. 1).

The health services and the ICU have been under a marked stress with a high demand for beds.



**FIGURE 1.** Risk factors of ventilator-associated pneumonia in COVID-19. ARDS, acute respiratory distress syndrome; MV, mechanical ventilation.

Organizational factors, such as nurse-to-patient ratio, increase workload, patients treated in non-ICU dedicated areas, the use of personal protective equipment (PPE) could have an impact on the risk of infection and cross-contamination [11]. But the rate of multidrug-resistant (MDR) pathogens in VA-LRTI in SARS-CoV-2 was lower than in other patients under invasive mechanical ventilation [2<sup>■</sup>,11,24]. Moreover, the compliance with hand hygiene during the pandemic seemed to be high, as some studies showed a marked increase in consumption of the alcohol-based hand rub solution [14]. However, these factors (low MDR and high alcohol-based hand rub solution consumption) were not determinant in the high incidence of VA-LRTI in COVID-19.

COVID-19 that need invasive mechanical ventilation present on the one side longer duration of mechanical ventilation and on the other side a higher incidence of ARDS than non-COVID-19 patients, both recognized as risk factors for VAP [2<sup>■</sup>,14,24]. In addition, the use of prone position was very frequent that is also associated with an increased risk of microaspiration [26]. Males, vasopressors and ECMO were also been identified as potential risk factors of VA-LRTI in COVID-19 [14,15,24].

Severe COVID-19 infection is associated with impaired immune response [4,6,7,27] that are known risk factors of VAP as well as the use of immunosuppressive therapies like corticosteroids [20,21<sup>■</sup>]. In COVID-19, the data concerning the impact of immunosuppressive therapies on VA-LRTI rates is conflicting. We showed that although the rate of adjuvant therapy with corticosteroids was similar in COVID-19 and influenza patients, the

duration and dose were higher in COVID-19 patients that could have an impact on the higher incidence of VA-LRTI [2<sup>■</sup>]. Apart from higher risk of VAP, immunosuppression and corticosteroids were also identified as risk factors for invasive pulmonary Aspergillosis [8<sup>■</sup>,14,28]. However, these findings were not reproduced by others [11,14,24].

### Impact of VA-LRTI on outcomes

Previous studies, performed in general ICU populations, showed an increased mortality rate in VAP patients [29,30]. A large meta-analysis was performed on individual data from 6284 patients included in randomized controlled trials of VAP prevention [31]. The overall attributable mortality of VAP was 13%, with higher rates for surgical patients and patients with a mid-range severity score at admission. Attributable mortality was mainly caused by prolonged exposure to the risk of dying due to increased length of ICU stay. However, other studies suggested that mortality attributable to VAP is even lower [32].

Few data are available on the impact of VAP on outcomes in COVID-19 patients. In a study performed in ARDS patients requiring ECMO [15], a mortality rate of 30% was reported in this population. However, this study was performed in a single centre, the number of patients with SARS-CoV-2 infection was small ( $N=50$ ), and no comparison was performed with mortality rate in SARS-CoV-2 patients with no VAP. Our group performed a planned ancillary study of the multicentre European coVAPid cohort, described above [33<sup>■</sup>]. VAP was associated with significantly higher risk for 28-day

mortality in SARS-CoV-2 [adjusted hazard ratio 1.70 (95% CI 1.16–2.47),  $P=0.006$ ], and influenza groups [1.75 (1.03–3.02),  $P=0.045$ ], but not in the no viral infection [1.07 (0.64–1.78),  $P=0.79$ ]. In addition, VAP was also associated with significantly longer duration of mechanical ventilation and ICU length of stay in COVID-19 patients. No significant difference was found in heterogeneity of outcomes related to VAP between the three groups, suggesting that the impact of VAP on mortality was not different between study groups. Further studies are required to confirm these findings and better understand the relationship between VAP and mortality in COVID-19 patients.

### Future research and areas of uncertainty

The use of corticosteroids has been a matter of debate over the last two/three decades in patients with pneumonia and ARDS [34]. And recent studies presented conflicting results and two systematic reviews and meta-analysis were published within the last 2 years [35,36]. Both agreed that corticosteroids decreased the mortality in patients with ARDS and, although one suggested that independently of the aetiology corticosteroids were associated with secondary infections, the other found that their use did not increase secondary infections such as nosocomial pneumonia; however, based on the trial sequential analysis, the authors could not exclude false-positive (type I) error. When we look at patients with severe community-acquired pneumonia, there is some evidence towards a better outcome if using corticosteroids as per a recent review however the largest study to date is still to be published. This is an over 500 patients, multicentric RCT that aimed to evaluate the use of corticosteroids for 20 days. The authors did not find a survival benefit [37].

The use of corticosteroids has been considered as a potential alternative adjuvant treatment in patients with COVID-19 with some good evidence; however, there are still some questions that remain open: Are all the corticosteroids the same, which is the timing to start? For how long? As powerful immunosuppressants, these all are relevant questions as they will benefit the inflammatory response in the phases of the disease of high inflammation; however, it is likely that if the patients are critically ill, in some cases, multiorgan failure and death can occur and corticosteroid use may lead to adverse effects, including hyperglycaemia, muscle atrophy, delirium and immunosuppression that could increase even further the risk of secondary infections.

In addition, some large studies published in patients with COVID-19 have still unresolved issues: selection bias due to patients being referred and

randomized in the study, a high number of excluded patients (close to 2000 individuals), ascertain bias due to the open-label design and the most important, no report of nosocomial infections. Consequently, although corticosteroids beneficially might decrease the COVID-19 hyperinflammatory response, individual analysis to determine immune signatures are urgently needed as it has been previously observed in patients treated with hydrocortisone for septic shock [38]. For instance, some clinical [39] and immune phenotypes [40] have been recently published and they may have implications for the design of therapeutics for COVID-19.

Another area of current discovery is the use of further immunosuppressant drugs on top of corticosteroids as they are now considered as a standard of care for patients for COVID-19. A potential target was some IL6 receptor antagonists such as tocilizumab. More than 160 studies have been published including observational studies and case series/reports. With a focus on RCT, there are currently eight published trials, three double blind and five open label. In the COVACTA study (double-blind), conducted in nine countries at 62 hospitals with 438 hospitalized patients randomly assigned to receive tocilizumab or placebo did not find any benefit regarding the clinical status improvement on an ordinal scale at day 28 [41]. On the contrary, the REMAP-CAP trial demonstrated a benefit in outcomes in an international, multifactorial, adaptive platform trial (open label), including survival, with the IL6 receptor antagonists tocilizumab and sarilumab in critically ill patients with COVID-19 [42]. There were nine serious adverse events in the tocilizumab group, none in the sarilumab group and 11 in the control arm but surprisingly no major concerns about secondary infections. All the other RCTs, either double blind or open label, there are no significant survival benefits. And a RCT (NCT04403685) was terminated early for safety reasons (potential higher mortality). This is surprising as when compared to recently published nonrandomized study. Kimmig *et al.* found that patients who received tocilizumab had higher mortality. This might be a selection bias related to the type of patients that received tocilizumab, but it is impressive that receiving tocilizumab was associated with a higher risk of secondary bacterial (48.1 vs. 28.1%;  $P=0.029$ ) and fungal (5.6 vs. 0%;  $P=0.112$ ) infections [43]. It is therefore not surprising that the drug is commercialized with the following warning: do not administer tocilizumab during an active infection, including localized infections. If a serious infection develops, interrupt tocilizumab until the infection is controlled. It is of note that also there are some studies that have suggested that treatment



with tocilizumab might favour the persistence of the SARS-CoV-2 virus and secondary infections [44]. Our group clearly showed, in a multicentre European study, that the incidence of VAP in COVID-19 was 36% [2<sup>••</sup>] that is higher than in influenza (22%) or without viral infections (16%). Probably, on the basis of the REMAP-CAP and COVACTA trials show mixed results for IL-6 blockade in COVID-19, we should be very careful to use if we suspect that the patient has a co-infection.

An important remark might be the area related to the body's viral control. Bermejo-Martin *et al.* [45] demonstrated that there was an uncontrolled viral replication in the pathogenesis of COVID-19. These authors found that SARS-CoV-2 RNAemia and viral RNA load in plasma are associated with critical illness in COVID-19 [45]. Furthermore, autopsies from COVID-19 patients demonstrate viral particles and viral RNA in different organs that represent viral dissemination in patients who died [46]. Some immunological patterns might explain why patients with severe COVID-19 impaired ability to control viral replication in critically ill patients. There are some Phase 2 and 3 studies ongoing with immunomodulation agents however this opens the discussion of why, so far, antiviral drugs have not shown clinical benefit to treat COVID-19 under mechanical ventilation [47], although showing significant benefit in less severe patients [48,49].

## CONCLUSION

In comparison with other severe diseases, COVID-19 patients are clearly at an increased risk of ICU-acquired infections, such as VA-LRTI. The mechanisms underlying this increased rate is not well understood being hypothesized the presence of humoral and cellular immune depression as potential contributors. Although superinfections have not been adequately monitored in most studies and trials assessing immunosuppressive therapies, there are some data pointing to higher rates of VA-LRTI as well as an increased risk of Aspergillosis. Moreover, VA-LRTI is also associated with poor outcomes, although the impact is not different in comparison with patients with influenza and no-viral infection under mechanical ventilation.

Future studies are needed to assess the impact of different preventive strategies on secondary pneumonias as well as the true risk and impact on outcomes of immunosuppressive therapies in COVID-19 patients.

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## Conflicts of interest

P.P., I.M.L. and S.N. have no conflicts of interest related to this topic.

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- of outstanding interest

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